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TITLE OF THE INVENTION (280 characters max)

HIGH-ENERGY CYCLODEXTRIN COMPLEXES

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HIGH-ENERGY CYCLODEXTRIN COMPLEXES

Cyclodextrins are a group of structurally related saccharides which are formed by enzymatic cyclization of starch by a group of amylases termed glycosyltransferases. Cyclodextrins are cyclic oligosaccharides, consisting of (α-1,4)-linked α-D-glucopyranose units, with a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are cone-shaped. The primary hydroxyl groups of the sugar residues are located on the narrow end of the formed cone while the wider face contains the secondary hydroxyl groups. The most common naturally occurring cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively. Of these three derivatives, β-cyclodextrin appears to be the most useful pharmaceutical complexing agent due to its cavity size, availability, low cost and other properties. However, γ-cyclodextrin is much more soluble in aqueous solutions than β-cyclodextrin and it possesses relatively good complexing abilities. Thus, for certain pharmaceutical formulations γ-cyclodextrin can be a better excipient than β-cyclodextrin. While it is thought that, due to steric factors, cyclodextrins having fewer than 6 glucopyranose units do not exist, cyclodextrins containing more than 8 units have been identified but their complexing abilities are generally lower than those of β-cyclodextrin and, thus, they are of less pharmaceutical interest. The natural cyclodextrins, in particular β-cyclodextrin, have limited aqueous solubility and their complex formation with lipophilic drugs often result in precipitation of solid drug-cyclodextrin complexes. Thus, the solubility of β-cyclodextrin in water is only about 18.5 mg/ml at room temperature. This low aqueous solubility is, at least partly, associated with strong intramolecular hydrogen bonding in the cyclodextrin crystal lattice. Substitution of any of the hydrogen bond-forming hydroxyl groups, even by hydrophobic moieties such as methoxy groups, will increase the aqueous solubility of β-cyclodextrin. In addition, since these manipulations frequently produce large numbers of isomeric products, chemical modification can transform the crystalline cyclodextrins into amorphous mixtures increasing their aqueous solubility (J. Pitha, J. Milecki, H.

Fales, L. Pannell and K. Uekama, "Hydroxypropyl-β-cyclodextrin: preparation and characterization; effects on solubility of drugs", *Int. J. Pharm.*, 29, 73-82 (1986)). For example, isomeric mixtures of 2-hydroxypropyl-β-cyclodextrin are obtained by treating a base-solubilized solution of β-cyclodextrin with propylene oxide. The aqueous solubility of 2-hydroxypropyl-β-cyclodextrin is over 60 g/100 ml (K.-H. Frömming and J. Szejtli, *Cyclodextrins in pharmacy* (Kluwer Academic Publishers, Dordrecht, the Netherlands, 1994); J. Pitha, J. Milecki, H. Fales, L. Pannell and K. Uekama, "Hydroxypropyl-β-cyclodextrin: preparation and characterization; effects on solubility of drugs", *Int. J. Pharm.*, 29, 73-82 (1986)). These cyclodextrin systems resemble, therefore, other pharmaceutical starches such as hydroxypropyl cellulose in terms of the complexity of their composition. Both the molar substitution, i.e. the average number of propylene oxide molecules that have reacted with one glucopyranose unit, and the location of the hydroxypropyl groups on the β-cyclodextrin molecule will affect the complexation properties of the 2-hydroxypropyl-β-cyclodextrin mixture. Other cyclodextrin derivatives of current pharmaceutical interest include the analogous hydroxypropyl derivatives of α- and γ-cyclodextrin, sulfoalkylether cyclodextrins such as sulfobutylether β-cyclodextrin, alkylated cyclodextrins such as the randomly methylated β-cyclodextrin, and various branched cyclodextrins such as glucosyl- and maltosyl-β-cyclodextrin. Some of the commercially available cyclodextrins are listed in **Table 2** hereinbelow.

In recent years cyclodextrins and their applications in pharmaceutical preparations have been extensively reviewed (T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997); T. Loftsson and M.E. Brewster, "Pharmaceutical applications of cyclodextrins. I. Drug solubilisation and stabilisation", *J. Pharm. Sci.* 85(10), 1017-1025 (1996); R.A. Rajewski and V.J. Stella, "Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery", *J. Pharm. Sci.* 85(11), 1142-1169 (1996); T. Irie and K. Uekama, "Pharmaceutical applications of cyclodextrins. 3. Toxicological issues and safety evaluation", *J. Pharm. Sci.*, 86(2), 147-162 (1997); V.J. Stella and R.A. Rajewski, "Cyclodextrins: their future in drug formulation and delivery", *Pharm. Res.*, 14(5), 556-567 (1997)).

Preparation of cyclodextrin inclusion complexes

In aqueous solutions, cyclodextrins form complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug molecule, or more frequently, by some lipophilic portion of the drug structure. The drug molecule is then called the guest molecule. The cyclodextrin cavity is relatively hydrophobic due to the presence of the skeletal carbons and ethereal oxygens which comprise the cavity. Since the water molecules located inside the cavity cannot satisfy their hydrogen-bonding potential, they are of higher enthalpy than bulk water molecules located in the solution. The main driving force for complex formation, at least in the case of β-cyclodextrin and its derivatives, appears to be the release of these enthalpy-rich water molecules from the cavity which lowers the energy of the system (T. Loftsson and M.E. Brewster, "Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilisation", *J. Pharm. Sci.*, 85, 1017-1025 (1996)). Once included in the cyclodextrin cavity, the guest molecules may be dissociated through complex dilution, by replacement of the included guest by some other suitable molecule (such as dietary lipids or bile salts in the GI tract) or, if the complex is located in close approximation to a lipophilic biological membrane (such as the mucosal membrane of the GI tract), the guest may be transferred to the matrix for which it has the highest affinity. Importantly, since no covalent bonds are formed or broken during the drug-cyclodextrin complex formation, the complexes are in dynamic equilibrium with free drug and cyclodextrin molecules.

Various methods have been applied to the preparation of drug-cyclodextrin complexes (F. Hirayama and K. Uekama, "Methods of investigating and preparing inclusion compounds", in *Cyclodextrins and Their Industrial Uses*, D. Duchêne, Ed. (Editions de Santé, Paris, France, 1987), pp. 131-172; T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997)). In solution, the complexes are usually prepared by addition of an excess amount of the drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated (for periods of up to one week at the desired temperature) and then filtered or centrifuged to form a clear drug-cyclodextrin complex solution.

Since the rate determining step in complex formation is often the phase to phase transition of the drug molecule, it is sometimes possible to shorten this process by formation of supersaturated solutions through sonication followed by precipitation. For preparation of the solid complexes, the water is removed from the aqueous drug-cyclodextrin solutions by evaporation or sublimation, e.g. spray-drying or freeze-drying. Other methods can also be applied to prepare solid drug-cyclodextrin complexes including kneading methods, co-precipitation, neutralization and grinding techniques (F. Hirayama and K. Uekama, "Methods of investigating and preparing inclusion compounds", in *Cyclodextrins and Their Industrial Uses*, D. Duchêne, Ed. (Editions de Santé, Paris, France, 1987), pp. 131-172). In the kneading method, the drug is added to an aqueous slurry of a poorly water soluble cyclodextrin such as β-cyclodextrin. The mixture is thoroughly mixed, often at elevated temperatures, to yield a paste which is then dried. This technique can frequently be modified so that it can be accomplished in a single step with the aid of commercially available mixers which can be operated at temperatures over 100 °C and under vacuum. The kneading method is a cost-effective means for preparing solid cyclodextrin complexes of poorly water-soluble drugs. Co-precipitation of cyclodextrin complex through addition of organic solvent is also possible. Unfortunately, the organic solvents used as precipitants can interfere with complexation which makes this approach less attractive than the kneading method. However, we have discovered that some organic solvents under some specific conditions, e.g. 10% (v/v) aqueous acetic acid solution, can enhance the complexation. Solid complexes of ionizable drugs can sometimes be prepared by the neutralization method wherein the drug is dissolved in an acidic (for basic drugs) or basic (for acidic drugs) aqueous cyclodextrin solution. The solubility of the drug is then lowered through appropriate pH adjustments (i.e. formation of the unionized drug) to force the complex out of solution. Finally, solid drug-cyclodextrin complexes can be formed by the grinding of a physical mixture of the drug and cyclodextrin and then heating the mixture in a sealed container to 60 to 90 °C (Y. Nakai, K. Yamamoto, T. Oguchi, E. Yonemochi and T. Hanawa, "New methods for preparing inclusion compounds. IV. Enhancement of combining molar ratio by using a ground mixture

in heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin and benzoic acid system", *Chem. Pharm. Bull.*, 39, 1532-1535 (1991)).

Methods for enhancing cyclodextrin complexation

For a variety of reasons including cost, production capabilities and toxicology, the amounts of cyclodextrin which can be used in most drug formulations is limited (T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997)). For example, the ideal weight of solid oral dosage forms, such as tablets, is between 100 and 500 mg. Even at high drug incorporation rates, one gram of a solid drug-cyclodextrin complex would only contain between 100 and 250 mg of the drug, assuming a drug with a molecular weight between 200 and 400 g/mol and a cyclodextrin with a molecular weight of between 1200 and 1500 g/mol. Thus even under the best condition, cyclodextrin complexation will result in a 4- to 10-fold increase in the formulation bulk. This limits the use of cyclodextrins in solid oral dosage forms to relatively potent drugs which possess good complexing properties. Likewise, the maximum cyclodextrin concentration in isotonic solutions is between 20 and 25% meaning that for some drugs, a parenteral system is not apparently practical. It is therefore important to develop methods which can be used to enhance the efficiency of drug-cyclodextrin complexation.

If one drug molecule (D) forms a complex with one cyclodextrin molecule (CD), then the complexation efficiency ([D-CD]/[CD]) will be equal to the intrinsic solubility of the drug (S_o) times the stability constant of the drug-cyclodextrin complex (K_C). In aqueous cyclodextrin solutions saturated with drug, the concentration of free drug ([D]) is approximately equal to S_o. Thus, increased complexation efficiency can be obtained by either increasing S_o or by increasing K_C or by increasing both simultaneously. See **FIG. 1**. The following is a short summary of the various methods which have been used to enhance drug solubility in cyclodextrin-containing systems (T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997)). See **FIG. 1**.

Organic solvents. Addition of organic solvents, such as ethanol, to the aqueous complexation media increases S_0. However, this frequently leads to decreased efficacy due to a significant decrease in the apparent K_C. The organic solvent molecules can compete with the drug molecules for a space in the cyclodextrin cavity which then results in a decrease in the apparent stability of the drug-cyclodextrin complex (i.e. decrease in K_C). Thus, addition of organic solvents frequently decreases the efficacy. However, we have discovered that some solvents, under some specific conditions, can enhance S_0 without having significant effect on K_C. See Example 5 below.

The effect of drug ionization. Unionized drugs frequently form more stable cyclodextrin complexes than their ionic counterparts (R. Krishnamoorthy and A.K. Mitra, "Complexation of weak acids and bases with cyclodextrins: Effects of substrate ionisation on the estimation and interpretation of association constants", *Int. J. Pharm. Advances*, 1, 330-343 (1996)). However, it is sometimes possible to enhance cyclodextrin solubilization of ionizable drugs by appropriate pH adjustments. For example, at room temperature (25 °C), the solubility of phenytoin (pKa 8.1) in water is only 18 μg/ml at pH 4.9 and 32 μg/ml at pH 8.0 (P.A. Schwartz, C.T. Rhodes and J.W. Cooper, "Solubility and ionisation characteristics of phenytoin", *J.Pharm.Sci.*, 66, 994-997 (1977)). Addition of 25% (w/v) 2-hydroxypropyl-β-cyclodextrin to the aqueous solutions increases the solubility of phenytoin to 5.0 mg/ml at pH 4.9 and 6.4 mg/ml at pH 8.0, which is 280- and 200-fold solubility enhancement, respectively (T. Loftsson and N. Bodor, "Effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol", *Acta Pharm. Nord.*, 1, 185-194 (1989)). Although the stability constant of the phenytoin-cyclodextrin complex is much larger for the drug in the unionized form than for the anionic form, it is possible to obtain much higher total solubility by adding cyclodextrin to the aqueous solution and at the same time increasing the pH (F.A. Menard, M.G. Dedhiya and C.T. Rhodes, "Studies of the effect of pH, temperature and ring size on the complexation of phenytoin with cyclodextrins", *Pharm. Acta Helv.*, 63, 303-308 (1988)). Similar results have been reported for the cyclodextrin solubilization of prazepam, acetazolamide and

sulfamethoxazole (T. Loftsson, T.K. Gudmundsdóttir and H. Fridriksdóttir, "The influence of water-soluble polymers and pH on hydroxypropyl-β-cyclodextrin complexation of drugs", *Drug Devel. Ind. Pharm.*, 22, 401-405 (1996)), and for dihydroergotamine mesylate (H. Helm, B.W. Müller and T. Waaler, "Complexation of dihydroergotamine mesylate with cyclodextrin derivatives: Solubility and stability in aqueous solution", *Eur.J.Pharm.Sci.*, 3, 195-201 (1995)). Ionization of an ionizable drug molecule increases S_0 and although some decrease in K_C is generally observed (due to the ionzation of the drug molecule), the increase in S_0 is frequently more than enough to compensate for the decrease, resulting in enhanced complexation efficacy.

The acid-effect. Addition of certain low molecular weight acids, such as acetic, citric, malic, or tartaric acid, to aqueous complexation media can enhance cyclodextrin solubilization of basic drugs through increase in both S_0 and K_C. For example, at room temperature (25 °C), the solubility of medazepam (pKa 6.2) in water is about 0.1 mg/ml at pH 8.0, at which the drug is unionized, and about 3.3 mg/ml in 10% (v/v) aqueous acetic acid solution (pH 3.8), at which the drug is protonated. Addition of 4% (w/v) 2-hydroxypropyl-β-cyclodextrin to the aqueous solutions increases the solubility of medazepam to about 0.5 mg/ml in water and to approximately 10 mg/ml in the acetic acid solution, which represent a 5- and 3-fold solubility enhancement, respectively (T. Loftsson and N. Bodor, "Effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol", *Acta Pharm. Nord.*, 1, 185-194 (1989)). It has been reported that it is possible to enhance the complexation of various basic drugs through formation of drug-hydroxy acid-cyclodextrin ternary complexes or salts (A. Selva, E. Redenti, M. Pasini, P. Ventura and B. Casetta, "Study of the salts of organic hydroxy acids of the terfenadine β-cyclodextrin inclusion complex in solution by mass spectrometry", *J. Mass Spectrom.*, 30, 219-220 (1994); É. Fenyvesi, M. Vikmon, J. Szemán, J. Szejtli, P. Ventura and M. Pasini, "Enhancement of the drug solubilizing capacity of hydroxypropyl-β-cyclodextrin by ternary complex formation", in *The 7th Cyclodextrin Symposium*, T. Osa, Ed. (Business Center for Academic Societies Japan, Tokyo, Japan, 1994), pp. 414-418;

M. Vikmon, J. Szemán, J. Szejtli, M. Pasini, E. Redenti and P. Ventura, "Terfenadine/cyclodextrin/hydroxyacid multicomponent complexes", in *The 7th Cyclodextrin Symposium*, T. Osa, Ed. (Business Center for Academic Societies Japan, Tokyo, Japan, 1994), pp. 480-483; P. Chiesi, P. Ventura, M. Pasini, J. Szejtli and M. Vikmon, Italian Patent Appl. No. MI 93 A 000141, 29 January 1993).

Water-soluble polymers. It has been shown that various pharmaceutical polymers, such as water-soluble cellulose derivatives and other rheological agents, can form complexes with cyclodextrins and that such complexes possess physicochemical properties distinct from those of individual cyclodextrin molecules (Thorsteinn Loftsson, "Cyclodextrin/drug complexation", U.S. Patent No. 5,324,718 (Jun. 28, 1994); Thorsteinn Loftsson, "Cyclodextrin complexation", E.P.A. Publication No.: 579,435 A1 (Jan. 19, 1994); Thorsteinn Loftsson, "Cyclodextrin Complexation", U.S. Patent No. 5,472,954 (December 5, 1995); T. Loftsson, H. Fridriksdóttir, A.M. Sigurdardóttir and H. Ueda, "The effect of water-soluble polymers on drug-cyclodextrin complexation", *Int.J.Pharm.*, 110, 169-177 (1994); G. Ganzerli, L. van Santvliet, E. Verschuren and A. Ludwig, "Influence of beta-cyclodextrin and various polysaccharides on the solubility of fluorescein and on the rheological and mucoadhesive properties of ophthalmic solutions", *Pharmazie*, 51, 357-362 (1996)). In aqueous solutions, water-soluble polymers increase the solubilizing effect of cyclodextrins on various hydrophobic drugs by increasing the apparent stability constants of the drug-cyclodextrin complexes. For example, the solubilizing effect of a 10% (w/v) 2-hydroxypropyl-β-cyclodextrin solution on a series of drugs and other compounds was increased from 12 to 129% when 0.25% (w/v) polyvinylpyrrolidone was added to the aqueous cyclodextrin solution (T. Loftsson, H. Fridriksdóttir, A.M. Sigurdardóttir and H. Ueda, "The effect of water-soluble polymers on drug-cyclodextrin complexation", *Int.J.Pharm.*, 110, 169-177 (1994)). Addition of 0.10% (w/v) polyvinylpyrrolidone to the aqueous complexation medium resulted in about 45% increase in the apparent stability constant (K_c) of the hydrocortisone - 2-hydroxypropyl-β-cyclodextrin complex. To

obtain this solubilization enhancement the solutions have to be heated to 120-140°C for 20 to 40 minutes.

This increase in K_C enhances the complexation efficiency and, thus, less cyclodextrin is needed to solubilize a given amount of a drug when small amounts of the described water-soluble polymers are present in the aqueous complexation media. This can be illustrated in the case of incorporation of carbamazepine and hydrocortisone into γ-cyclodextrin. An excess of the drug to be tested was added to an aqueous 5% (w/v) γ-cyclodextrin solution, containing no polymer or a small amount of a water-soluble polymer, and the suspension formed was heated in an autoclave (120°C for 20 minutes). After equilibration at room temperature for at least three days, the suspensions were filtered through an 0.45 μm membrane filter, the filtered drug -γ-cyclodextrin solution freeze-dried and the drug content of the dry complex powder determined by an HPLC method. The carbamazepine content was 0.98 g per 100 g dry complex powder when no polymer was used and increased to 2.22 g per 100 g complex powder when 0.10% (w/v) hydroxypropyl methylcellulose was added to the aqueous complexation media. This represents a 127% increase in complexation. In the case of hydrocortisone, the content was 6.44 g per 100 g complex powder when no polymer was present increasing to 16.5 g per 100 g with the addition of 0.10% (w/v) hydroxypropyl methylcellulose, representing a 156% increase. Addition of water-soluble polymers to the aqueous complexation media (and heating to 130-140°C for 20-40 min) increases the apparent K_C and, thus, increased efficiency is observed (T. Loftsson and H. Fridriksdóttir, "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of β-cyclodextrin", *International Journal of Pharmaceutics* (in print)).

Combination methods. It is often possible to enhance cyclodextrin complexation even further by using several different methods simultaneously to enhance the cyclodextrin complexation. For instance, prazepam is a benzodiazepine with a pK_a of about 3. 2-Hydroxypropyl-β-cyclodextrin has solubilizing effect on both the unionized and the ionized form of the drug, and, as expected, hydroxypropyl methylcellulose has a synergistic effect on the solubilization. However, the synergistic effect was more pronounced for the ionized form (FIG. 2)

(T. Loftsson, T.K. Gudmundsdóttir and H. Fridriksdóttir, "The influence of water-soluble polymers and pH on hydroxypropyl-β-cyclodextrin complexation of drugs", *Drug Devel. Ind. Pharm.*, 22, 401-405 (1996)). **FIG. 2** illustrates the effect of ionization and hydroxypropyl methylcellulose (HPMC) on the 2-hydroxypropyl-β-cyclodextrin (HPβCD) solubilization of prazepam (pK_a 3) in aqueous buffer solutions.

<u>β-Cyclodextrin</u>. While the use of β-cyclodextrin is hampered by its low aqueous solubility, many water-soluble drugs, and other water-soluble compounds, are able to solubilize β-cyclodextrin in much the same way that water-soluble cyclodextrins are capable of solubilizing water-insoluble drugs (H. Fridriksdóttir and T. Loftsson, "Solubilization of β-cyclodextrin", *Proceedings of the 8th International Cyclodextrins Symposium*, (J. Szejtli and L. Szente, Eds.), Kluwer Academic Publishers, Dordrecht, 1996, pp. 373-376; T. Loftsson and H. Fridriksdóttir, "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of β-cyclodextrin", *International Journal of Pharmaceutics* (in print)). At room temperature (approx. 23 °C), the solubility of β-cyclodextrin in water is 18.5 mg/ml, which increases to about 21 mg/ml when 0.10% (w/v) hydroxypropyl methylcellulose is present in the solution. When a solution is saturated with both β-cyclodextrin and a lipophilic drug, the total solubility of β-cyclodextrin increases, representing both the intrinsic solubility of the starch and the solubility of the complex. Thus, the total solubility of β-cyclodextrin in a saturated solution containing carbamazepine has been determined to be 28 mg/ml when no polymer is present but 55 mg/ml when 0.10% (w/v) hydroxypropyl methylcellulose is present (T. Loftsson and H. Fridriksdóttir, "The effect of water-soluble polymers on the aqueous solubility and complexing abilities of β-cyclodextrin", *International Journal of Pharmaceutics* (in print)). This increase was obtained when the complexation efficiency was enhanced by the heating method, i.e. heating of a aqueous suspension in a sealed container to 120-140°C for 20-40 minutes. Comparable results were obtained when carbamazepine was replaced by methazolamide or sulphamethoxazole. The polymer not only increases the aqueous solubility of β-cyclodextrin but also enhances the complexation, making a 5% (w/v) β-cyclodextrin solution as powerful a solubilizer as a 10 to 15% (w/v) 2-

hydroxypropyl-β-cyclodextrin solution. Furthermore, addition of polymers can significantly enhance the efficiency of the complexation when a solid complex powder is produced by the kneading method at elevated temperatures.

Permeability of drugs through biological membranes

Most drugs permeate biological membranes (such as the skin barrier (*stratum corneum*), the eye cornea, and mucosal membranes) by the mechanism of passive diffusion. The driving force of such drug transport is the gradient of chemical potential (μ) along the direction of diffusion, i.e. spontaneous flow from a region of higher chemical potential to one of lower chemical potential (T. Loftsson, "Experimental and theoretical model for studying simultaneous transport and metabolism of drugs in excised skin", *Arch. Pharm. Chemi, Sci. Ed.*, 10, 17-24 (1982); T. Higuchi, "Physical chemical analysis of percutaneous absorption process from creams and ointments", *J. Soc. Cosmet. Chem.*, 11, 85-97 (1960)). The chemical potential can be described by the following equation:

$$\mu = \mu^{o} + RT\ln a$$

where μ^{o} is the chemical potential in a chosen reference state, R is the gas constant, T is the temperature in degree Kelvin, and a is the thermodynamic activity of the drug in the aqueous donor phase. Thus, enhanced drug permeability through a biological membrane is obtained from donor phases which are saturated by the drug. In fact, it has been shown that the permeability can be enhanced even further through formation of supersaturated drug solutions (M.A. Pellett, M.S. Roberts and J. Hadgraft, "Supersaturated solutions evaluated with an in vitro stratum corneum tape stripping technique", *Int. J. Pharm.*, 151, 91-98 (1997)). In such vehicle systems, the drug molecules have very high thermodynamic activity which significantly enhances their chemical potential and, thus, the drug molecules have great tendency to partition into the biological membrane and, subsequently, to permeate through the membrane.

The cyclodextrin molecules are relatively large (molecular weight ranging from almost 1000 to over 1500), with a hydrated outer surface, and under normal conditions, cyclodextrin molecules will only permeate biological membranes with considerable difficulty (R.A. Rajewski and V.J. Stella, "Pharmaceutical applications of

cyclodextrins. 2. In vivo drug delivery", *J. Pharm. Sci.* 85(11), 1142-1168 (1996); T. Irie and K. Uekama, "Pharmaceutical applications of cyclodextrins. 3. Toxicological issues and safety evaluation", *J. Pharm. Sci.* 86(2), 147-162 (1997); K.-H. Frömming and J. Szejtli, *Cyclodextrins in pharmacy*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1994; T. Loftsson and N. Bodor, "The effect of cyclodextrins on percutaneous transport of drugs", in: E. W. Smith and H. I. Maibach (Eds.), *Percutaneous Penetration Enhancers*, CRC Press, Boca Raton, Florida, 1995, pp. 335-342; T. Loftsson and E. Stefánsson, "Effect of cyclodextrins on topical drug delivery to the eye", *Drug Dev. Ind. Pharm.* 23(5), 473-481 (1997)). It is generally recognized that cyclodextrins act as true carriers by keeping the hydrophobic drug molecules in solution and deliver them to the surface of the biological membrane, e.g. skin, mucosa or the eye cornea, where they partition into the membrane. The relatively lipophilic membrane has low affinity for the hydrophilic cyclodextrin molecules and therefore they remain in the aqueous membrane exterior, e.g. the aqueous vehicle system, salvia or the tear fluid. Conventional penetration enhancers, such as alcohols and fatty acids, disrupt the lipid layers of the biological barrier. Cyclodextrins, on the other hand, act as penetration enhancers by increasing drug availability at the surface of the biological barrier. However, cyclodextrins can lower the thermodynamic activity of a lipophilic drug through enhancement of drug solubility in an aqueous vehicle. Thus, maximum permeability is observed when just enough cyclodextrin is used to solubilize all the drug in the vehicle. Addition of too much cyclodextrin, more than is needed to solubilize the drug, will decrease the permeability (T. Loftsson and A.M. Sigurdardottir, "The effect of polyvinylpyrrolidone and hydroxypropyl methylcellulose on HPβCD complexation of hydrocortisone and its permeability through hairless mouse skin", *Eur. J. Pharm. Sci.*, 2, 297-301 (1994); A.M. Sigurdardottir and T. Loftsson, "The effect of polyvinylpyrrolidone on cyclodextrin complexation of hydrocortisone and its diffusion through hairless mouse skin", *Int. J. Pharm.*, 126, 73-78 (1995)). Addition of water-soluble polymer, such as polyvinylpyrrolidone, enhanced the drug complexation and increased the drug permeability through the skin. Comparable effects have been observed after topical application to the eye (P. Jarho, A. Urtti, D.W. Pate, P. Suhonen and T. Jarvinen, "Increase in aqueous solubility,

stability and in vitro corneal permeability of anandamide by hydroxypropyl-β-cyclodextrin", *Int. J. Pharm.*, 137, 209-216 (1996); J.K. Kristinsson, H. Fridriksdottir, S. Thorisdottir, A.M. Sigurdardottir, E. Stefansson and T. Loftsson, "Dexamethasone-cyclodextrin-polymer co-complexes in aqueous eye drops", *Inv. Ophthalmol. Vis. Sci.*, 37(6), 1199-1203 (1996). The water-soluble polymers apparently increase the thermodynamic activity of the drug molecules at the surface of the biological membrane.

Description of the invention

It is possible to enhance the cyclodextrin (CD) complexation efficacy of drugs (D), and other "guest" molecules, by either increasing the apparent stability constant (K_C) of the drug-cyclodextrin complex (D-CD) or increasing the apparent intrinsic solubility (S_0) of the drug. For example, K_C can be increased by addition of water-soluble polymers to the aqueous complexation media and S_0 can be increased by ionization of the drug molecule, as described previously. However, increased complexation efficacy by itself does not necessarily result in increased drug availability in the aqueous complexation media or increased drug availability from solid drug-cyclodextrin complexes. On the other hand, if the drug-cyclodextrin complexes are prepared under conditions which ensure enhanced complexation and if the complexation efficacy decreases upon administration, then enhanced drug availability will be observed. Thus, the present invention involves: i) enhancement of the complexation efficacy and ii) reduction of the complexation efficacy after administration. For example, it is possible to enhance the complexation efficacy of many ionizable drugs by preparing the complexes at pH where the drug is ionized but obtain decreased efficacy upon administration due to pH changes and consequent decreased ionization. One example of such a drug is phenytoin (pKa 8.1). Its solubility in water at room temperature (25 °C) is only 18 μg/ml at pH 5 and 32 μg/ml at pH 8 (P.A. Schwartz, C.T. Rhodes and J.W. Cooper, "Solubility and ionisation characters of phenytoin", *J. Pharm. Sci.*, 66, 994-997 (1977)). Addition of 25% (w/v) 2-hydroxypropyl-β-cyclodextrin to the aqueous solutions increases the solubility of phenytoin to 5.0 mg/ml at pH 5 and 6.4 mg/ml at pH 8, which is 280- and 200-fold

solubility enhancement, respectively. Although the apparent stability constant (K_C) of the phenytoin-cyclodextrin complex is much larger for the drug in the unionized form than for the anionic form, it is possible to obtain much higher total solubility by increasing the apparent intrinsic solubility (S_O) of the drug (T. Loftsson and N. Bodor, "Effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol", *Acta Pharm. Nord.*, 1, 185-194 (1989)). However, if the pH 8.0 solution was placed in an environment which would decrease the pH from 8 to 5 (e.g. topical application to the skin), then a supersaturated solution would be formed which would result in enhanced drug availability (e.g. it would result in enhanced transdermal drug delivery). Other means to enhance S_O include reversible derivation (e.g. prodrug formation) of the guest molecule and addition of certain low molecular weight acids. The value of K_C can, for example, be increased by addition of certain low molecular weight acids, by addition of water-soluble polymers to the aqueous complexation media or by using mixed solvent systems such as aqueous 10% (v/v) acetic acid. For example, addition of the polymers and heating in an autoclave (to 120-140°C for 20-40 minutes) does not only increase the complexation but it has also been shown to enhance transdermal and transcorneal drug delivery (T. Loftsson and A.M. Sigurdardottir, "Cyclodextrins as skin penetration enhancers", in J. Szejtli and L. Szente (Eds.) *Proceedings of the Eighth International Symposium on Cyclodextrins*, Kluwer Academic Publishers, 1996, pp. 403-406; T. Loftsson and E. Stefansson, "Effect of cyclodextrins on topical drug delivery to the eye", *Drug Devel. Ind. Pharm.*, 23(5), 473-481 (1997)). As shown in **Table 1** below, it is not enough to add the polymers to the complexation medium. Addition of polymers to the unheated vehicles did not enhance the transdermal delivery of enalaprilat. However, heating the vehicles after addition of the polymers resulted in significant enhancement. The effect of the polymers on the transdermal delivery of enalaprilat can, at least partly, been explained by decreased complexation efficacy (i.e. decrease in K_C) at the skin surface.

Table 1. The effect of heating on transdermal delivery of enalaprilat from 10% (w/v) HPβCD solutions at pH 5.0 containing 2.5% enalaprilat in a suspension. The concentration of dissolved enalaprilat was between 2.0 and 2.3% (w/v).

Donor phase (w/v per cent)	Flux ($mg\ h^{-1}\ cm^{-2}$) Un-heated	Heated	Ratio
HPβCD	18±2	-	-
HPβCD, 0.25% PVP	16±6	23±7	1.4
HPβCD, 0.10% HPMC	14±3	37±12	2.6

The following table (**Table 2**) lists some of the currently available cyclodextrins contemplated for use in the present invention.

Table 2. Some of the currently available cyclodextrins obtained by substitution of the OH-groups located on the edge of the cyclodextrin ring. Since both the number of substituents and their location will affect the physicochemical properties of the cyclodextrin molecules, such as their aqueous solubility and complexing abilities, each derivative listed should be regarded as a group of closely related cyclodextrin derivatives.

Type	α-Cyclodextrin derivatives	β-Cyclodextrin derivatives	γ-Cyclodextrin derivatives
Alkylated:			
	Methyl	Methyl	Methyl
		Ethyl	
	Butyl	Butyl	Butyl
			Pentyl
Hydroxylalkylated:			
		Hydroxyethyl	Hydroxyethyl
	2-Hydroxypropyl	2-Hydroxypropyl	2-Hydroxypropyl
		2-Hydroxybutyl	
Esterified:			
	Acetyl	Acetyl	Acetyl
		Propionyl	
		Butyryl	
	Succinyl	Succinyl	Succinyl
		Benzoyl	
		Palmityl	
		Toluenesulfonyl	
Esterified and alkylated:			
		Acetyl methyl	
		Acetyl butyl	
Branched:			
	Glucosyl	Glucosyl	Glucosyl
	Maltosyl	Maltosyl	Maltosyl
Ionic:			
	Carboxymethyl ether	Carboxymethyl ether	Carboxymethyl ether
		Carboxymethyl ethyl	
	Phosphate ester	Phosphate ester	Phosphate ester
		3-Trimethylammonium-2-hydroxypropyl ether	
		Sulfobutyl ether	
Polymerized:			
	Simple polymers	Simple polymers	Simple polymers
	Carboxymethyl	Carboxymethyl	Carboxymethyl

Particularly preferred cyclodextrins for use herein are hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin and γ-cyclodextrin.

In preferred aspects of the present invention, the drug for use herein is one having a structure comprising at least one heterocyclic ring. The heterocyclic ring generally has a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms. While each hetero ring atom can be nitrogen, oxygen or sulfur, heterocycles having at least one nitrogen ring atom are preferred. Preferably, the drug has at least one heterocyclic ring which is a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal.

Especially desirable drugs for use in accord with the present invention are benzodiazepines. Benzodiazepines contain a benzene ring fused with a diazepine ring which is a 7-membered ring with nitrogen atoms in positions 1 and 4. By way of example, the chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine, the chemical name of midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine and that of triazolam is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine. Thus, all of these compounds have the 1,4-benzodiazepine structure with a double bond between nitrogen atom number 4 and carbon atom number 5 (which gives the molecule a cyclic imine structure). The benzodiazepines are cyclic imines. They are all basic, i.e. they are proton acceptors. Preferred benzodiazepines for use herein are alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam and lorazolam. Especially preferred are midazolam, alprazolam, clonazepam, lorazepam and triazolam.

Another group of preferred drugs for use herein consists of the barbituric acid derivatives. The barbituric acids contain a 2,4,6-trihydroxypyrimidine (also called 2,4,6-trioxohexahydropyrimidine) ring in their structure, a 6-member ring with

nitrogen in positions 1 and 3. Thus, the chemical name of barbital if 5,5-diethyl-2,4,6(1H,3H,5H)-pyrimidinetrione and that of phenobarbital is 5-ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione. The barbituric acids can be characterized as cyclic amides of lactams (cyclid amides are called lactams) or imides (which are nitrogen analogues of cyclic anhydrides). Barbituric acids are weak acids. Preferred barbituric acid derivatives are barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, cyclohexenylallylthiobarbituric acid and their salts. Thiopental is 5-ethyldihydro-5-(1-methylbutyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione, i.e. one = O moiety in the barbituric acid structure has been replaced by = S.

Yet another group of preferred drugs for use in the present invention consists of the hydantoins. Hydantoins are, like barbituric acids, cyclic urea derivatives. The ring-opened acyl derivatives of hydantoins and barbituric acids are sometimes called ureides. Both hydantoins and barbituric acids can form urea upon hydrolysis. Hydantoins contain a 2,4-imidazolidinedione ring in their structure, a 5-membered ring with nitrogen in positions 1 and 3. The chemical name of, for example, phenytoin, is 5,5-diphenyl-2,4-imidazolidinedione. Hydantoins are closely related to barbituric acids and are acids like them.

Still another group of preferred drugs for use in the present invention consists of pyrazole derivatives. The expression "pyrazole derivatives" as used herein includes drugs containing a pyrazole ring, 3-pyrazoline ring or pyrazolidine ring in their structure, all of which 5-membered rings with nitrogens in positions 1 and 2. These compounds are either basic or acidic. Preferred pyrazole derivatives for use herein include phenazone, phenylphenazone, metamidazole, phenylbutazone, oxyphenbutazone and sulfinpyrazone.

Yet another group of drugs preferred for use herein consists of imidazole derivatives. The expression "imidazole derivatives" as used herein includes drugs containing an imidazole, imidazoline or imidazolidine ring in their structure. These

are 5-membered rings with nitrogen atoms in positions 1 and 3. These compounds are either basic or acidic. Preferred compounds of this type include histamine, miconazole, pilocarpine, naphazoline and clonidine.

Another group of preferred drugs for use in this invention are pyrimidine derivatives. These drugs contain a 6-membered ring with nitrogen atoms in positions 1 and 3. These derivatives are usually basic. Preferred pyrimidine derivatives include thiamine, trimethoprim, orotic acid, methylthiouracyl and prothiouracyl.

Still another group of preferred drugs for use herein are purine derivatives, which contain purine, that is, imidazo(4,5-d)pyrimidine, in their structures. These drugs are frequently basic but some of them are acidic. Preferred purine derivatives include caffeine, theophylline, etophylline, proxyphylline and theobromine.

Cyclic drugs having heterocyclic rings characterized as enamines, lactones, lactams, thiolactams, anhydrides, imides, imines, hemiacetals and hemiketals are thus appropriate for use in preferred embodiments of the invention, in which ring opening of the heterocyclic ring takes place.

In one aspect of the present invention, there is provided a method for enhancing the complexation efficacy of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said drug to chemically reversible ring-opening so that at least a portion thereof is in ring-opened form, and complexing said drug with cyclodextrin.

In a related aspect of the invention, there is provided a method for enhancing the complexation efficacy of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine,

lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion of said drug. The complexation is advantageously conducted at a pH level which affords ring-opening of at least 5% by weight of said drug. Preferably the complexation is conducted at a pH level of below about 5.

In one preferred embodiment, the drug is a basic drug, especially a benzodiazepine, and the complexation is conducted at a pH level of below about 5. It is also preferred that the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin. It is also preferred that the benzodiazepine is alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam or loprazolam; and that the cyclodextrin-drug complex thus obtained be formulated as a nasal spray, sublingual tablet or parenteral solution, especially when formulated suitable for use in producing a sedative, anti-anxiety, anticonvulsant or muscle relaxant effect, most especially as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and/or maintain anaesthesia or to induce a hypnotic effect. In especially preferred embodiments, the benzodiazepine is midazolam, alprazolam, clonazepam, lorazepam or triazolam; the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin; and the complexation is conducted at a pH level below about 5, preferably between about 3 and about 5.

In another embodiment of the present method utilizing chemically reversible ring-opening described above, the drug is an acidic drug.

In yet another embodiment of the present method utilizing chemically reversible ring-opening described above, the drug is a barbituric acid derivative, a hydantoin, a pyrazole derivative, an imidazole derivative, a pyrimidine derivative or a purine derivative. When the drug is a barbituric acid derivative, it is preferably

barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, or cyclohexenylallylthiobarituric acid, or a salt thereof. When the drug is a hydantoin, it is preferably phenytoin. When the drug is a pyrazole derivative, it is preferably phenazone, propylphenazone, metamidazole, phenylbutazone, oxyphenbutazone or sulfinpyrazone. When the drug is an imidazole derivative, it is preferably histamine, miconazole, pilocarpine, naphazoline or clonidine. When the drug is a pyrimidine derivative, it is preferably thiamine, trimethoprim, orotic acid, methylthiouracyl or prothiouracyl. When the drug is a purine derivative, it is preferably caffeine, theophylline, etophylline, proxyphylline or theobromine.

In another aspect of the present invention, there is provided a method for enhancing the availability of a drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imine, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion of said drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy. The complexation is generally conducted at a pH level which affords ring-opening of at least 5% by weight of the drug. Preferably, the complexation is conducted at a pH level of below about 5, especially between about 3 and about 5. The cyclodextrin is preferably hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin. The drug is preferably a benzodiazepine, especially midazolam, alprazolam, clonazepam, lorazepam or triazolam. The cyclodextrin-drug complex is preferably administered

in the form of an aqueous solution or a hydrogel, particularly as a nasal spray or nasal drops, or as a parenteral solution. As a nasal spray of a benzodiazepine, the aqueous solution is advantageously brought to a pH level of below about 6, preferably below about 4.7, most especially to a pH between about 3 and about 4.7. When administered as a solid, the cyclodextrin-drug complex is preferably formulated as a tablet for oral, buccal or sublingual administration. The water may be removed from the aqueous complexation medium after formation of the cyclodextrin-drug complex.

In still another aspect of the present invention, there is provided a method for enhancing the availability of a basic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said basic drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said basic drug to complexation in an aqueous medium at a pH level below the pKa+2 value of said basic drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy. Preferably, the basic drug is a benzodiazepine. Benzodiazepines of particular interest are alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam and loprazolam. Particularly preferred benzodiazepines are alprazolam, midazolam, clonazepam, lorazepam and triazolam. The cyclodextrin-benzodiazepine complex obtained in the complexation step is preferably formulated as a nasal spray, sublingual tablet or parenteral solution, which is preferably administered in an effective sedative, anti-anxiety, anticonvulsant or muscle relaxant amount, particularly as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and/or maintain anaesthesia or to induce a

hypnotic effect. In this general aspect of the invention, the pH level of the aqueous complexation medium is advantageously selected so that it also affords ring-opening of at least 5% by weight of the drug. For the benzodiazepines, the complexation is preferably conducted at a pH level of below about 5, most preferably between about 3 and about 5. Also in this general aspect of the invention, in one preferred embodiment, the complexation is carried out in the presence of from about 0.001 to about 5% (weight/volume) of a pharmacologically inactive, pharmaceutically acceptable water-soluble polymer at a temperature of from about 30°C to about 150°C. Preferably, the polymer is a cellulose derivative or a polyvinyl polymer; more preferably, the polymer is methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl ethylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone. An especially preferred cellulose derivative is hydroxypropyl methylcellulose. A method for enhancing drug-cyclodextrin complexation utilizing a pharmacologically inactive water-soluble polymer is described in Loftsson United States Patents No. 5,324,718 and No. 5,472,954, both of which are incorporated by reference herein in their entireties and relied upon. In another preferred embodiment of this general aspect of the invention, the complexation is also carried out in the presence of acetic acid and/or one or more pharmaceutically acceptable salts of acetic acid, the acetate-water ratio of the aqueous complexation medium being from about 1:1000 to about 2:1, preferably from about 1:100 to about 1:1, more preferably from about 1:20 to about 1:4. Preferably, the drug is midazolam and the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

In yet another aspect of the present invention, there is provided a method for enhancing the availability of an acidic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said acidic drug having a structure comprising at least one heterocyclic ring having a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring

atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said acidic drug to complexation in an aqueous medium at a pH level above the pKa-2 value of said acidic drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy. Preferably, the pH level of the aqueous complexation medium is selected such that it also affords ring-opening of at least 5% by weight of said drug.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in no way limitative of the invention.

Example 1

Phenytoin (5,5-diphenylhydantoin) is a water-insoluble weak acid (pKa 8.1) which forms a somewhat water-soluble anion in alkaline solution. Solubility (S) of phenytoin at three different pH levels was determined in aqueous solutions containing various amounts of 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.9, i.e. (a) pH 2.74±0.18 (SD), (b) pH 7.55±0.12, and (c) pH 10.19±0.14. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed sonicated for one hour at room temperature (23°C). After equilibration at 25°C in a water-bath for three days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved phenytoin determined by a high pressure liquid chromatographic method (HPLC). **FIG. 3** illustrates the effect of pH on the phase-solubility of phenytoin (pKa 8.1) in aqueous HPβCD solutions at 25°C. The results set forth in **FIG. 3** show significant enhancement in the HPβCD solubilization (i.e. the efficacy of the complexation) of the drug at pH 10.19 where the drug is mainly in the ionized form. Formation of phenytoin-HPβCD complexes at pH 10.19 can result in enhanced bioavailability of phenytoin. For example, topical application of such a

solution to the skin will result in lowering of pH, which will decrease the efficacy of the complexation, which again will result in enhanced permeability of phenytoin into and through the skin. Also, formation of phenytoin-HPβCD complexes at pH of about 10 (e.g. in aqueous ammonia solutions) and lyophilization of the complex will result in phenytoin-HPβCD complex powder which can, for example, be formulated into tablets. The bioavailability of phenytoin from such tablets will be enhanced compared to the phenytoin availability from tablets containing phenytoin-HPβCD complex prepared at lower pH (e.g. at pH 2.7 or 7.6).

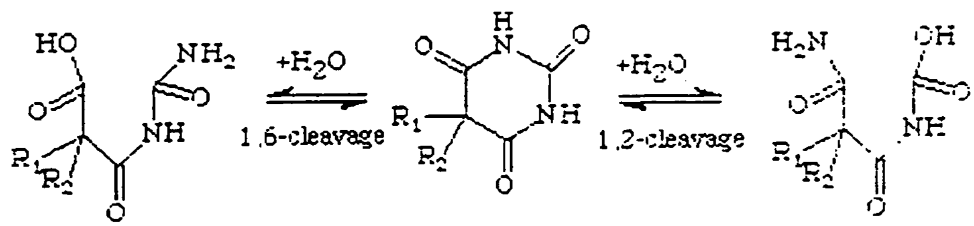
Example 2

Alprazolam is a water-insoluble weak base (pKa 2.41) which forms a somewhat water-soluble cation in acidic solution. Solubility (S) of alprazolam at several different pH levels was determined in aqueous solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved alprazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 4** illustrates the effect of pH on the solubility of alprazolam (pKa 2.4) in aqueous 10% (w/v) HPβCD solutions at room temperature. The results set forth in **FIG. 4** show significant enhancement in the HPβCD solubilization (i.e. the efficacy of the complexation) of the drug at a pH at which the drug is mainly in the ionized form. The sharp increase in the solubility can, however, only partly be explained by the ionization of the alprazolam molecule.

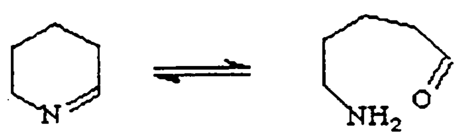
Example 3

Several drugs which have a nitrogen-containing heterocycle in their structure are known to undergo reversible ring-opening which frequently is pH dependent. For

example, barbituric acids undergo reversible ring cleavage (H.J. Roth, K. Eger and R. Troschütz, *Pharmaceutical Chemistry. Volume 2. Drug Analysis.* Ellis Horwood, 1991, pp. 308-309):



Another example of such reversible ring-opening is the opening of cyclic imines through formation of an aldehyde or ketone and a primary amine:



An example of such structure is the 1*H*-1,4-diazepine ring which, for example, is an essential structure of the benzodiazepine derivatives. These structural changes are pH-dependent and reversible, and it is known that the open form frequently co-exists with the closed one in several commercial products. One example is the *iv* solution of midazolam (Dormicum™ from Roche) where the drug is partly in the open form (J.H. Kanto, "Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia", *Pharmacotherapy*, 5(3), 138-155 (1985)). However, the open form of midazolam is rapidly converted to the closed one upon *iv* administration.

We have determined the effect of pH and cyclodextrins, i.e. HPβCD MS 0.3, sulfobutylether β-cyclodextrin (SBEβCD) with degree of substitution (DS) = 6.4, α-cyclodextrin (αCD) and γ-cyclodextrin (γCD) on the ring-opening of several benzodiazepines. The cyclodextrin concentration was 10% (w/v) and the benzodiazepine concentration was 1×10^{-4} M. The concentration of the closed form was determined right after dissolving the benzodiazepine in the aqueous cyclodextrin solution and again 24 hours later (i.e. after equilibration at 23°C). Preliminary experiments had shown that equilibrium between the closed and the open form was attained within 3 hours at 23°C.

It is clear from the results displayed in **Table 3** below that a large fraction of the benzodiazepines (over 50% at pH below 2) are in the open form at low pH and that the fraction of open form frequently increases upon addition of cyclodextrin to the aqueous solution. For example, at pH 3 about 60% of alprazolam in aqueous HPβCD solution is in the open form. This will increase the apparent intrinsic solubility (S_O), which under these conditions will be the sum of the intrinsic solubilities of the open and the closed forms. This increase in S_O will result in enhanced complexation efficacy. The observed increase in the complexation efficacy will result in enhanced cyclodextrin solubilization of the benzodiazepines in aqueous solutions.

Table 3. The effect of pH and cyclodextrins on the fraction of the open form of several benzodiazepines at room temperature (approx. 23°C).

Benzodiazepine	Cyclodextrin	pH	Fraction open
Alprazolam (pKa 2.4)	None	2	0.82
		3	0.56
		4	0.33
	HPβCD	2	0.89
		3	0.60
		4	(0.06?)
	SBEβCD	2	0.96
		3	0.84
		4	0.33
	αCD	2	0.94
		3	0.79
		4	0.25
	γCD	2	0.81
		3	0.41
		4	0.42
Diazepam (pKa 3.3)	None	2	0.30
		3	0.23
		4	0.15
	HPβCD	2	0.65
		3	0.29
		4	(0.00?)
	SBEβCD	2	0.63
		3	0.56
		4	0.22
	αCD	2	0.67
		3	0.51
		4	(0.08?)
	γCD	2	0.41
		3	0.17
		4	0.13

Table cont. on next page.

Benzodiazepine	Cyclodextrin	pH	Fraction open
Midazolam (pKa 6.2?)	None	2	0.74
		3	0.28
		4	0.18
	HPβCD	2	0.56
		3	0.18
		4	(0.23?)
	SBEβCD	2	0.81
		3	0.39
		4	0.11
	αCD	2	0.79
		3	0.32
		4	0.10
	γCD	2	0.61
		3	0.21
		4	0.17
Triazolam (pKa ?)	None	2	0.53
		3	0.08
		4	0.00
	HPβCD	2	0.51
		3	0.09
		4	0.00
	SBEβCD	2	0.71
		3	0.25
		4	0.00
	αCD	2	0.75
		3	0.23
		4	0.00
	γCD	2	0.33
		3	0.01
		4	0.00

Example 4

Midazolam is a water-insoluble weak base (pKa 6.2) which forms a somewhat water-soluble cation in acidic solution. Solubility (S) of midazolam at several different pH levels was determined in: a) pure aqueous buffer solutions (i.e. without HPβCD and HPMC); b) aqueous buffer solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3; and c) aqueous solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3 and 0.10% (w/v) hydroxypropyl methylcellulose (HPMC) 4000. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved midazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 5** illustrates the effect of pH (i.e. the ring openings) on the solubility of midazolam (pKa 6.2) in pure aqueous buffer solutions, aqueous buffer solutions containing 10% (w/v) HPβCD, and aqueous buffer solutions containing both 10% (w/v) HPβCD and 0.10% (w/v) HPMC at room temperature.. The results set forth in **FIG. 5** show significant enhancement in the HPβCD solubilization (i.e. the efficacy of the complexation) of the drug at pH levels where the drug exists partly in the open form. Addition of HPMC significantly improves the efficacy.

Example 5

Solubility (S) of midazolam at several different pH levels was determined in: a) pure aqueous buffer solutions (i.e. without cyclodextrin, polymer or acetate); b) aqueous buffer solutions containing 10% (v/v) acetate as a co-solvent; c) aqueous buffer solutions containing 10% (w/v) sulfobutylether β-cyclodextrin (SBEβCD) and 10% (v/v) acetate as a co-solvent; and d) aqueous buffer solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD), 0.10% (w/v) hydroxypropyl methylcellulose (HPMC) and 10% (v/v) acetate as a co-solvent. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed was

heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved midazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 6** illustrates the effects of cyclodextrins, pH and 10% (v/v) acetate on the solubility of midazolam in aqueous solutions: pure aqueous buffer solution (▲); aqueous 10% (v/v) acetate solution (●); 10% (w/v) HPβCD solution containing 0.10% (w/v) HPMC in aqueous 10% (v/v) acetate solution (■); 10% (w/v) aqueous SBEβCD solution in aqueous 10% (v/v) acetate (♦). The results set forth in **FIG. 6** show that addition of 10% (v/v) acetate significantly improves the complexation. Addition of the acetate increases the value of S_0 without having any significant effect on the value of K_C, which significantly improves the complexation efficacy and, consequently, enhances the cyclodextrin solubilization of the drug. Midazolam carries a positive charge at acidic pH and, thus, the negatively charges SBEβCD forms a more stable complex than the uncharged HPβCD with midazolam at these conditions. Addition of 10% (v/v) acetate as a co-solvent resulted in a small decrease in the fraction of the open ring form of the drug.

While the invention has been described in terms of various preferred embodiments, the person skilled in the art will appreciate that various modifications, substitutions, omissions and changes can be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

1. A method for enhancing drug availability, when the drug is in a complex with cyclodextrin, by preparing the drug-cyclodextrin complexes under conditions which enhance the complexation efficacy, through elevation of the apparent intrinsic solubility (S_0) and/or increase in the value of the apparent stability constant (K_C) of the drug-cyclodextrin complex and subsequent decrease in S_0 and/or K_C upon administration.

2. A method for enhancing the availability of a cosmetic additive, food additive or agrochemical when in a complex with cyclodextrin by preparing their cyclodextrin complexes under conditions which enhance the complexation efficacy, through elevation of the apparent intrinsic solubility (S_0) and/or increase in the value of the apparent stability constant (K_C) of the drug-cyclodextrin complex and subsequent decrease in S_0 and/or K_C.

3. A method according to Claim 1 or 2, wherein the complexation efficacy of a basic guest molecule (i.e. proton acceptor) is enhanced through lowering the pH of the aqueous complexation media below the pKa+2 value of the guest molecule whereby the intrinsic solubility of guest molecule is increased.

4. A method according to Claim 1 or 2, wherein the complexation efficacy of an acidic guest molecule (i.e. proton donor) is enhanced through elevating the pH of the aqueous complexation above the pKa-2 value of the acidic guest molecule whereby the intrinsic solubility of the guest molecule is increased.

5. A method according to Claim 1 or 2, wherein the complexation efficacy of a guest is enhanced through addition of 0.001 to 5% (w/v) of acceptable water-soluble polymer whereby the apparent stability constant of the complex is increased.

6. A method according to Claim 1 or 2, wherein the complexation efficacy of a guest is enhanced through addition of acetate (acetic acid and/or its salts) to the aqueous complexation media where the acetate-water ratio is from 1:1000 to 2:1.

7. A method according to Claim 1 or 2, wherein the complexation efficacy is enhanced through addition of hydroxyacids, such as citric acid, lactic acid or malic acid, to the aqueous complexation media.

8. A method according to Claim 1 or 2, wherein the complexation efficacy is enhanced through formation of chemically reversible derivatization or prodrug formation.

9. A method according to Claim 8, wherein the chemically reversible derivatives are obtained by ring-opening of N-containing heterocycles, such as ring-opening of cyclic imines or amides.

10. A method according to Claim 9, wherein the parent drug is barbituric acid (e.g. barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbturic acid, cyclohexenylallylthiobarbituric acid or their salts), hydantoins (e.g. phenytoin), pyrazole derivative (e.g. phenazone. propylphenazone, metamidazole, phenylbutazone, oxyphenbutazone, or sulfinpyrazone), imidazole derivatives (e.g. histamine, miconazole, pilocarpine, naphazoline or clonidine), pyrimidine derivatives (e.g. thiamine, trimethoprim, orotic acid, methylthiouracyl or prothiouracyl), or purine derivatives (e.g. caffeine, theophylline, etophylline, proxyphylline or theobromine).

11. A method according to Claim 9, wherein the parent drug is a benzodiazepine derivative (e.g. alprazolam, brotizolam, chlordiazepoxide, clobazam,

clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, or temazepam).

12. A pharmaceutical composition comprising a cyclodextrin complex of a benzodiazepine prepared at pH below 5 and in which at least 5% of the total benzodiazepine is in the ring-open form.

13. A pharmaceutical composition according to Claim 5, 6, 11 or 12 where the pharmaceutical composition is an aqueous solution such as nasal spray, nasal drops, parenteral solution or hydrogel.

14. A pharmaceutical composition according to Claim 13 where the pharmaceutical composition is a nasal spray containing an aqueous solution of alprazolam or midazolam at pH below 6, preferably below 4.5.

15. A pharmaceutical composition according to Claim 5, 6, 11 or 12 where the pharmaceutical composition. such as conventional tablets or sublingual or buccal tablets, contains solid benzodiazepine-cyclodextrin complex.

16. A method according to Claim 1 through 7, where the water is removed after preparing the energized complex.

17. A method for enhancing the complexation efficacy of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said drug to chemically reversible ring-opening so that at least a portion thereof is in ring-opened form, and complexing said drug with cyclodextrin.

18. A method for enhancing the complexation efficacy of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion of said drug.

19. A method according to Claim 18, wherein the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

20. A method according to Claim 19, wherein the complexation is conducted at a pH level of below about 5.

21. A method according to Claim 19, wherein the drug is a basic drug.

22. A method according to Claim 21, wherein the complexation is conducted at a pH level of below about 5.

23. A method according to Claim 19, wherein the drug is a benzodiazepine.

24. A method according to Claim 23, wherein the complexation is conducted at a pH level of below about 5.

25. A method according to Claim 23, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

26. A method according to Claim 23, wherein the benzodiazepine is alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam or loprazolam.

27. A method according to Claim 26, followed by formulating the cyclodextrin-drug complex thus obtained as a nasal spray, sublingual tablet or parenteral solution.

28. A method according to Claim 27, wherein the nasal spray, sublingual tablet or parenteral solution is formulated to be suitable for use in producing a sedative, anti-anxiety, anticonvulsant or muscle relaxant effect.

29. A method according to Claim 28, wherein the nasal spray, sublingual tablet or parenteral solution is formulated to be suitable for use as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and maintain anaesthesia or to induce a hypnotic effect.

30. A method according to Claim 29, wherein the benzodiazepine is alprazolam, clonazepam, lorazepam, midazolam or triazolam.

31. A method according to Claim 26, wherein the complexation is conducted at a pH level below about 5.

32. A method according to Claim 31, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

33. A method according to Claim 31, wherein the benzodiazepine is midazolam, alprazolam, clonazepam, lorazepam or triazolam.

34. A method according to Claim 22, wherein the complexation is conducted at a pH level between about 3 and about 5.

35. A method according to Claim 24, wherein the complexation is conducted at a pH level between about 3 and about 5.

36. A method according to Claim 31, wherein the complexation is conducted at a pH level between about 3 and about 5.

37. A method according to Claim 33, wherein the complexation is carried out at a pH level between about 3 and about 5.

38. A method according to Claim 33, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

39. A method according to Claim 37, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

40. A method according to Claim 19, wherein the drug is an acidic drug.

41. A method according to Claim 19, wherein the drug is a barbituric acid derivative, a hydantoin, a pyrazole derivative, an imidazole derivative, a pyrimidine derivative or a purine derivative.

42. A method according to Claim 41, wherein the barbituric acid derivative is barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, or cyclohexenylallylthiobarituric acid, or a salt thereof.

43. A method according to Claim 41, wherein the hydantoin is phenytoin.

44. A method according to Claim 41, wherein the pyrazole derivative is phenazone, propylphenazone, metamidazole, phenylbutazone, oxyphenbutazone or sulfinpyrazone.

45. A method according to Claim 41, wherein the imidazole derivative is histamine, miconazole, pilocarpine, naphazoline or clonidine.

46. A method according to Claim 41, wherein the pyrimidine derivative is thiamine, trimethoprim, orotic acid, methylthiouracyl or prothiouracyl.

47. A method according to Claim 41, wherein the purine derivative is caffeine, theophylline, etophylline, proxyphylline or theobromine.

48. A method for enhancing the availability of a drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imine, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion of said drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy.

49. A method according to Claim 48, wherein the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

50. A method according to Claim 49, wherein the complexation is conducted at a pH level of below about 5.

51. A method according to Claim 50, wherein the drug is a benzodiazepine.

52. A method according to Claim 51, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

53. A method according to Claim 51, wherein the benzodiazepine is midazolam, alprazolam, clonazepam, lorazepam or triazolam.

54. A method according to Claim 53, wherein the complexation is carried out at a pH level between about 3 and about 5.

55. A method according to Claim 54, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

56. A method according to Claim 48, wherein the cyclodextrin-drug complex is administered in the form of an aqueous solution or a hydrogel.

57. A method according to Claim 56, wherein the cyclodextrin-drug complex is administered as a nasal spray or nasal drops.

58. A method according to Claim 56, wherein the cyclodextrin-drug complex is administered as a parenteral solution.

59. A method according to Claim 53, wherein the cyclodextrin-drug complex is administered in the form of an aqueous solution.

60. A method according to Claim 59, wherein the aqueous solution is at a pH level of below about 6 and is administered as a nasal spray.

61. A method according to Claim 60, wherein the pH level of the nasal spray is below about 4.7.

62. A method according to Claim 61, wherein the pH level of the nasal spray is between about 3 and about 4.7.

63. A method according to Claim 51, wherein the cyclodextrin-drug complex is administered as a solid.

64. A method according to Claim 63, wherein the solid cyclodextrin-drug complex is administered as a tablet formulated for oral, buccal or sublingual administration.

65. A method according to Claim 48, wherein the water is removed from the aqueous complexation medium after formation of the cyclodextrin-drug complex.

66. A method for enhancing the availability of a basic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said basic drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said basic drug to complexation in an aqueous medium at a pH level below the pKa+2 value of said basic drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy.

67. A method according to Claim 66, wherein the basic drug is a benzodiazepine.

68. A method according to Claim 66, wherein the benzodiazepine is alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam or loprazolam.

69. A method according to Claim 68, wherein the benzodiazepine is alprazolam, midazolam, clonazepam, lorazepam or triazolam.

70. A method according to Claim 68, the cyclodextrin-drug complex obtained in the complexation step being formulated as a nasal spray, sublingual tablet or parenteral solution.

71. A method according to Claim 70, wherein the nasal spray, sublingual tablet or parenteral solution is administered in an effective sedative, anti-anxiety, anticonvulsant or muscle relaxant amount.

72. A method according to Claim 71, wherein the nasal spray, sublingual tablet or parenteral solution is administered as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and maintain anaesthesia or to induce a hypnotic effect.

73. A method according to Claim 72, wherein the benzodiazepine is alprazolam, clonazepam, lorazepam, midazolam or triazolam.

74. A method according to Claim 67, wherein the pH level of the aqueous complexation medium is selected such that it also affords ring-opening of at least 5% by weight of said drug.

75. A method according to Claim 74, wherein the complexation is conducted at a pH level of below about 5.

76. A method according to Claim 75, wherein the complexation is carried out at a pH level between about 3 and about 5.

77. A method according to Claim 74, wherein the complexation is carried out in the presence of from about 0.001 to about 5% (weight/volume) of a pharmacologically inactive, pharmaceutically acceptable water-soluble polymer at a temperature of from about 30°C to about 150°C.

78. A method according to Claim 77, wherein the polymer is a cellulose derivative or a polyvinyl polymer.

79. A method according to Claim 78, wherein the polymer is methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl ethylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone.

80. A method according to Claim 79, wherein the cellulose derivative is hydroxypropyl methylcellulose.

81. A method according to Claim 74, wherein the complexation is also carried out in the presence of at least one member of the group consisting of acetic acid and its pharmaceutically acceptable salts, the acetate-water ratio of the aqueous complexation medium being from about 1:1000 to about 2:1.

82. A method according to Claim 81, wherein the drug is midazolam and the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

83. A method according to Claim 77, wherein the complexation is also carried out in the presence of at least one member of the group consisting of acetic acid and its pharmaceutically acceptable salts, the acetate-water ratio of the aqueous complexation medium being from about 1:1000 to about 2:1.

84. A method according to Claim 83, wherein the drug is midazolam and the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin or γ-cyclodextrin.

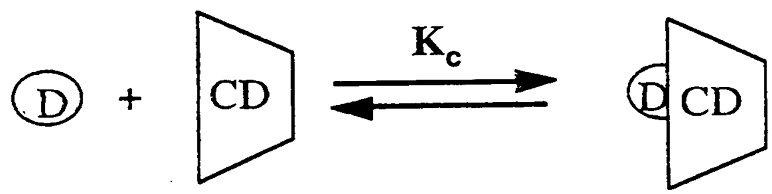
85. A method for enhancing the availability of an acidic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said acidic drug having a structure comprising at least one heterocyclic ring having a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said acidic drug to complexation in an aqueous medium at a pH level above the pKa-2 value of said acidic drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy.

86. A method according to Claim 85, wherein the pH level of the aqueous complexation medium is selected such that it also affords ring-opening of at least 5% by weight of said drug.

ABSTRACT OF THE DISCLOSURE

Methods for enhancing the complexation efficacy of a drug with cyclodextrin and for enhancing the availability of a drug following administration of a cyclodextrin-drug complex.

Fig. 1



$$K_c = \frac{[D\text{-}CD]}{[D]\,[CD]} \qquad [D] \approx S_o$$

(Aqueous CD solution saturated with the drug.)

$$\Rightarrow \textbf{Complexation efficacy} = K_C\,S_o = \frac{[D\text{-}CD]}{[CD]}$$

Fig. 2

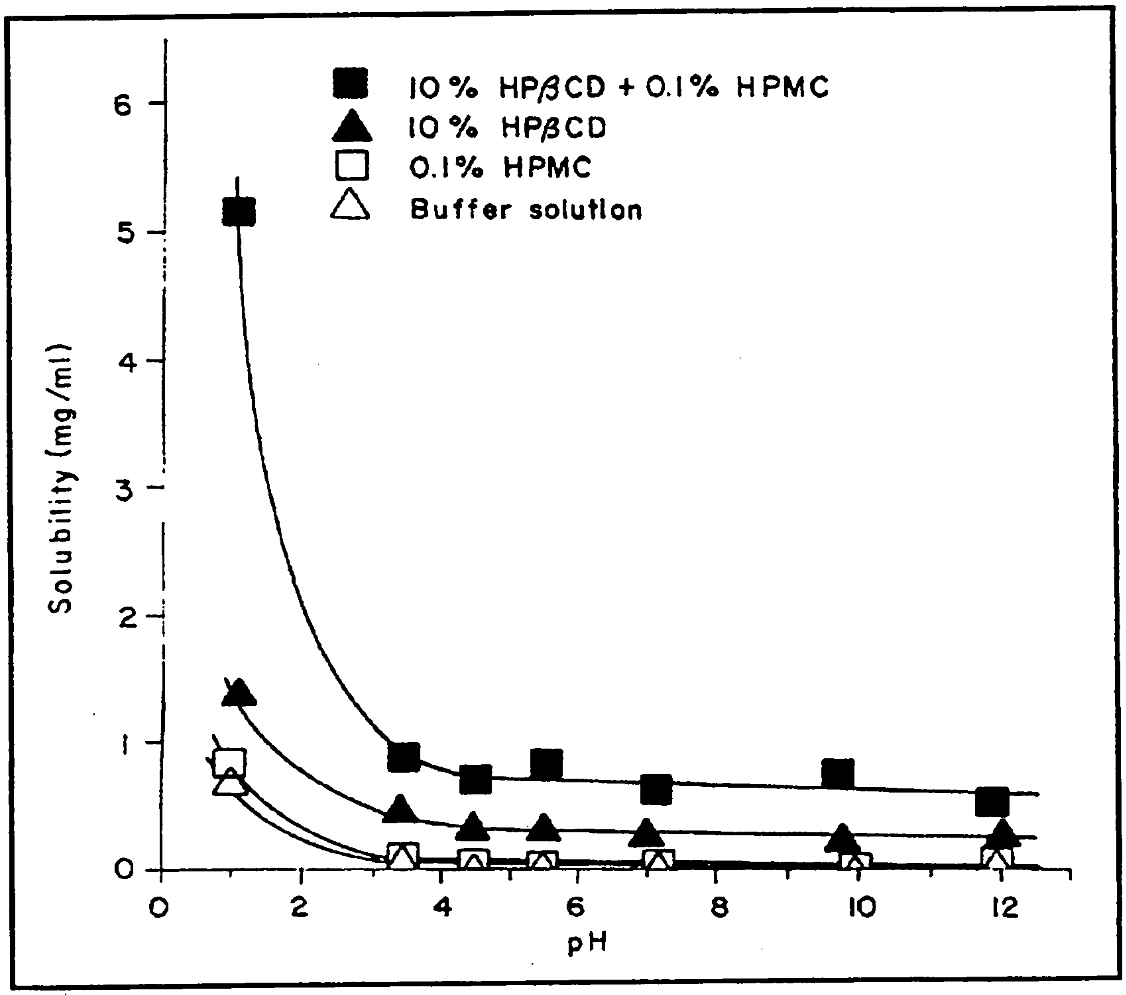
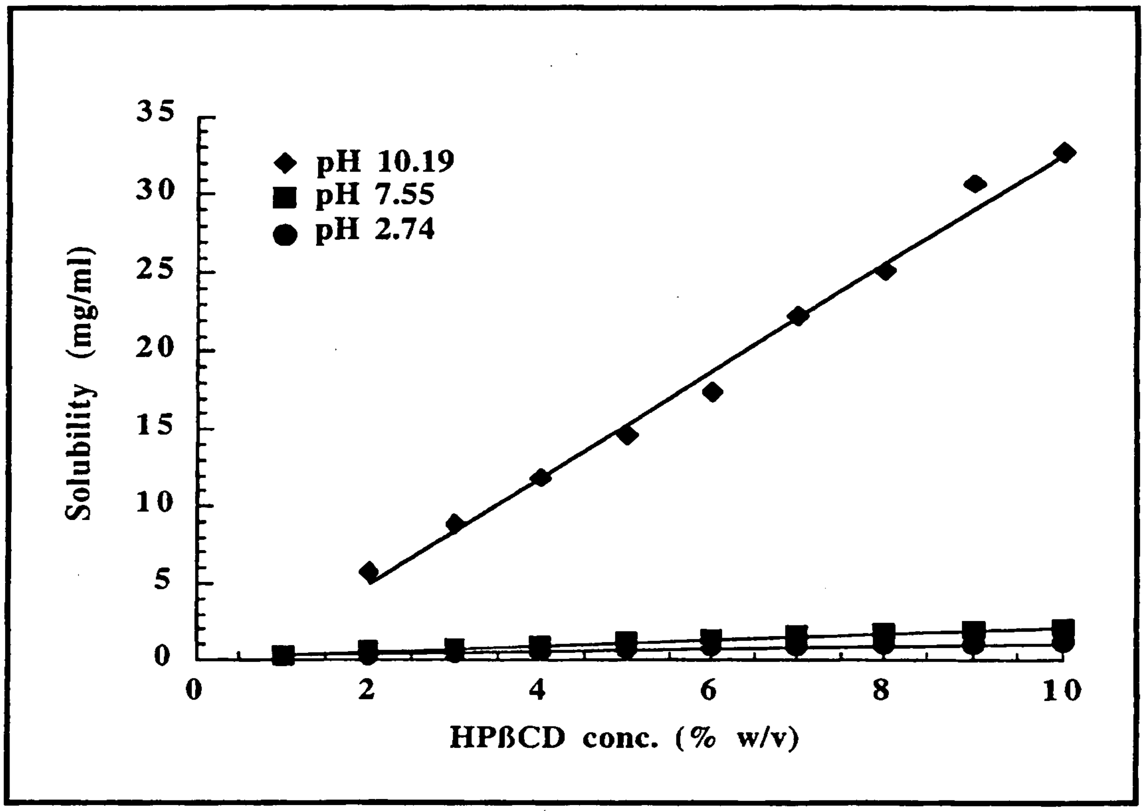

10 % HPβCD + 0.1% HPMC
10 % HPβCD
0.1% HPMC
Buffer solution
Solubility (mg/ml)
0
1
2
3
4
5
6
0
2
4
6
8
10
12
pH

Fig. 3



pH 10.19
pH 7.55
pH 2.74
Solubility (mg/ml)
35
30
25
20
15
10
5
0
0
2
4
6
8
10
HPßCD conc. (% w/v)

Fig. 4

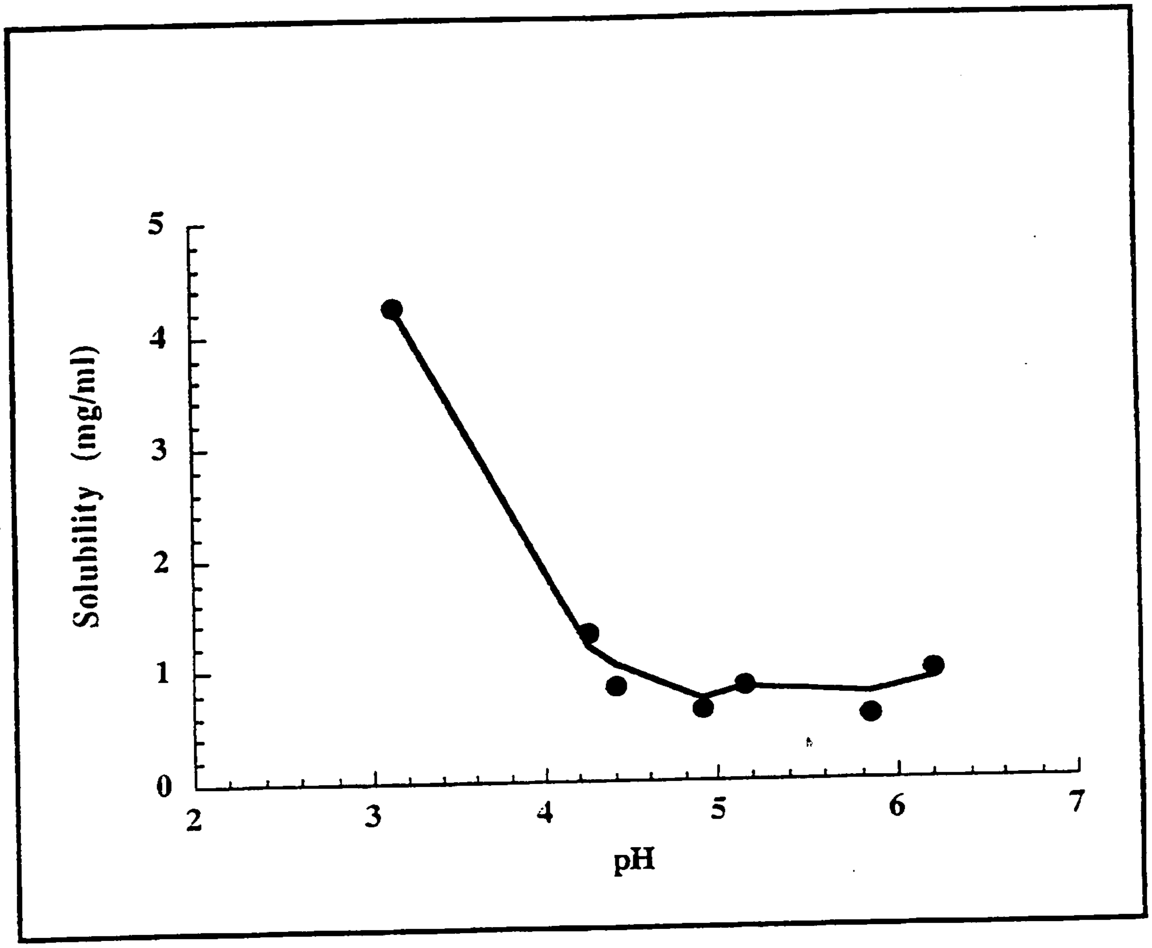


Fig. 5

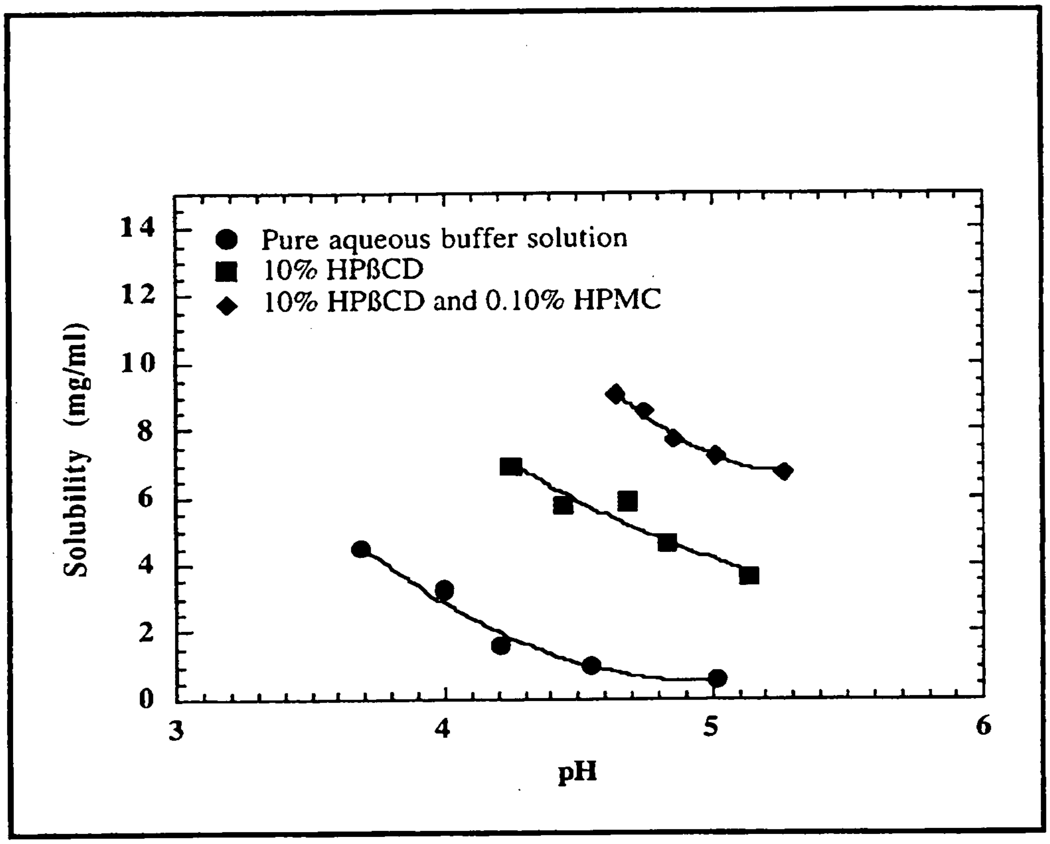

Pure aqueous buffer solution
10% HPßCD
10% HPßCD and 0.10% HPMC
Solubility (mg/ml)
14
12
10
8
6
4
2
0
3
4
5
6
pH

Fig. 6